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Fluctuating Asymmetry and Disorders of Developmental Origin

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Environmental and/or genetic stresses may cause a breakdown in developmental homeostasis, resulting in increased bilateral asymmetry of morphological traits. The degree of these deviations (termed "fluctuating asymmetry") is thought to correlate with the severity of the stress. If these stresses also play a role in the appearance of developmental disorders, then increased morphological asymmetry may serve as a risk marker for disorders of developmental origin. This would be possible if 1) the environmental stress that caused a breakdown in developmental stability also contributed to the appearance of the disorder, and/or 2) the genetic predisposition (liability) to the disorder and increased susceptibility to fluctuating asymmetry have a common cause. Although a number of authors have reported associations between increased fluctuating asymmetry and disorders of presumed developmental origin, the usefulness of fluctuating asymmetry as a risk marker has not been established. One obstacle to this assessment is the lack of odds ratios reported by previous authors. © 1996 Wiley-Liss, Inc.

KEY WORDS: fluctuating asymmetry, risk marker, developmental disorders, ontogeny

INTRODUCTION

Morphological asymmetry has traditionally been categorized into three types: fluctuating asymmetry, directional asymmetry, and antisymmetry [Van Valen, 1962]. Directional asymmetry describes the case where a morphological asymmetry is consistently biased to the same side of the body in different individuals (e.g., the consistent asymmetry of thoracic organs in humans). In antisymmetry, a trait is asymmetrical in all individuals, but whether the left or right side is larger varies among individuals. There is no clear human example of this, although handedness would provide a reasonable analogy [see also Yeo and Gangestad, 1993]. Fluctuating asymmetry shows random bilateral deviations from normal symmetry, with the larger side and the magnitude of the asymmetry varying among individuals. As most individuals are very nearly symmetrical, a histogram of left minus right differences is normally distributed with a mean of zero. These two criteria, normal distribution and a parametric mean of zero define fluctuating asymmetry [Van Valen, 1962]. Human examples of traits showing fluctuating asymmetry are the lengths of corresponding limbs or facial structures. In fact, anything that is normally considered identical on both sides of the body may exhibit fluctuating asymmetry. Obviously, while the direction of a trait showing fluctuating asymmetry is random with regards to the population as a whole, any asymmetry in a given individual will be biased to one side or the other. More than one type of asymmetry can exist concurrently in the same population. However, characters exhibiting either directional or antisymmetry should not be used for assessing fluctuating asymmetry [Palmer and Strobeck, 1992; Palmer et al., 1993].

Fluctuating asymmetry has long been used as a measure of the success of developmental homeostasis in countering environmental stress. The phenotypic expression of fluctuating asymmetry is presumably due to a complex series of interactions between the physical environment and the genetic constitution during ontogeny. Within the last 15 years, fluctuating asymmetry has attracted increasing interest in the fields of behavioural ecology, conservation biology, and quantitative genetics, as there is evidence to show that the level of observed fluctuating asymmetry in an organism is associated with sexual selection [Møller and Pomiankowski, 1993; Watson and Thornhill, 1994], environmental stress [Leary and Allendorf, 1989; Parsons, 1990, 1992], fitness (in the evolutionary sense) [Ueno, 1994; Thornhill, 1992; Naugler and Leech, 1994; Harvey and Walsh, 1993], physical performance [Manning and Ockenden, 1994], and morbidity of chromosomal,

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polygenic, or developmental origin in a wide range of species, including humans [Palmer and Strobeck, 1986; Livshits and Kobyliansky, 1991].

Regarding clinical diagnosis in humans, Livshits and collaborators stated ". . . fluctuating asymmetry of anthropomorphic traits might be a useful and sensitive measure of developmental instability in human ontogeny . . . it should be possible to use fluctuating asymmetry to predict appearance of, or predisposition to, congenital anomalies in ontogeny" [Livshits et al., 1988a]. Perhaps the most promising application of fluc*tuating* asymmetry in clinical medicine is in the analysis of liability for multifactorial disorders that fit a polygenic threshold model [Gottesman and Shields, 1967; McGue et al., 1983; Markow and Gottesman, 1989; Markow and Wandler, 1986; Woolf and Gianas, 1976, 1977]. Table I lists the clinical disorders for which increased fluctuating asymmetry has been reported. Despite the encouraging results of these papers, fluctuating asymmetry has not been widely applied to clinical medicine [Hoyme, 1993], and the promise of the utility of fluctuating asymmetry to clinical medicine has therefore remained largely unfulfilled. A major shortcoming in the literature on fluctuating asymmetry is that previous studies have simply reported the statistical significance of group comparisons, rather than stressing the potential of fluctuating asymmetry as a risk marker by reporting odds ratios. In this paper we review the etiology of fluctuating asymmetry and propose several models to explain the association between fluctuating asymmetry and disorders of developmental origin.

ETIOLOGY OF FLUCTUATING ASYMMETRY

Fluctuating asymmetry is considered to reflect the ability of an organism to maintain developmental homeostasis (stability) in the face of environmental perturbations (sometimes referred to as "developmental noise") [Palmer and Strobeck, 1986]. However, the relative importance of the genome and the environment in which it is acting have often been confused. It is known that environmental stress (e.g., temperature and chemical stresses) will result, *on average*, in a phenotype that exhibits increased fluctuating asymmetry [Beardmore, 1960; Parsons, 1990; Leary and Allendorf, 1989; Watson and Thornhill, 1994] (see Fig. 1). In humans, the effect of environmental stress is perhaps best exemplified by the finding of increased asymmetry in children exposed to alcohol in utero [Wilber et al., 1993; Kieser, 1992]. Interestingly, fluctuating asymmetry has not been found among children of mothers who smoked during pregnancy [Kieser and Groeneveld, 1994], even though smoking has been linked to other fetal development problems.

The fact that the same level of stress produces different fluctuating asymmetries in different individuals seems to indicate that the phenotypic outcome is being modified by a variable ability to buffer the effects of environmental perturbations, or as Livshits and Kobyliansky [1989] phrased it "a different sensitivity of the gene products to random fluctuations of the environment." Watson and Thornhill [1994] refer to this as "susceptibility" to fluctuating asymmetry (see Fig. 2). A critical distinction must be made here between a varying genetic susceptibility to fluctuating asymmetry and genetically *caused* asymmetry. Varying susceptibility (differing abilities to buffer developmental noise) are likely to occur among all individuals with non-identical genomes and may have several causes. A growing body of literature, for example, demonstrates a correlation between homozygosity and fluctuating asymmetry, with individuals who are more homozygous being on average less symmetrical [Brückner, 1976; Soulé,1979; Kat, 1982; Leary et al., 1983; Mitton and Grant, 1984; Danzmann et al., 1986; Wolff, 1987; Zouros and Foltz, 1987; Quattro and Vrijenhoeck, 1989; Blanco et al., 1990; Kartartser, 1990; Mitton, 1993]. This correlation could be explained either by the existence of overdominance (superior heterozygous allelle combinations; see Smouse [1986], Chakraborty [1987], Turelli and Ginzburg [1983], Zouros [1993], and Clarke [1993] for discussions of the relationship between heterozygosity and Darwinian fitness) or by the expression of an increased number of deleterious recessive alleles [Parsons, 1992; Clarke, 1992, 1993]. However, there is no clear evidence to support one explanation over the other. Presumably, either of these processes causes a potential disruption of developmental homeostasis, so that fluctuating asymmetry will appear at a lower level of stress as compared to normalindividuals. Another genetic mechanism may create susceptibility to fluctuating asymmetry in special circumstances. This is the interruption of co-adapted gene complexes and may be the mechanism responsible for the decreased develop-

TABLE I. Disorders Showing Increased Fluctuating Asymmetry

Disorder	Trait measured	Author(s)
Exposure to ethanol in utero	Odontometrics	Kieser [1992]
	Dermatoglyphics	Wilber et al. [1993]
Schizophrenia	Dermatoglyphics	Mellor [1992]; Markow and Wandler [1986]; Markow and Gottesman [1989]
Fragile (X) syndrome	Odontometrics	Peretz et al. [1988]
Down syndrome	Odontometrics	Garn et al. [1970]
	Odontometrics	Barden [1980b]
	Odontometrics	Townsend [1983, 1987]
Cleft lip/palate	Dermatoglyphics	Woolf and Gianas [1976]; Adams and Niswander [1967]
	Odontometrics	Sofaer [1979]; Adams and Niswander [1967]
Mental retardation	Odontometrics	Barden [1980a]
	Various traits	Malina and Buschang [1984]

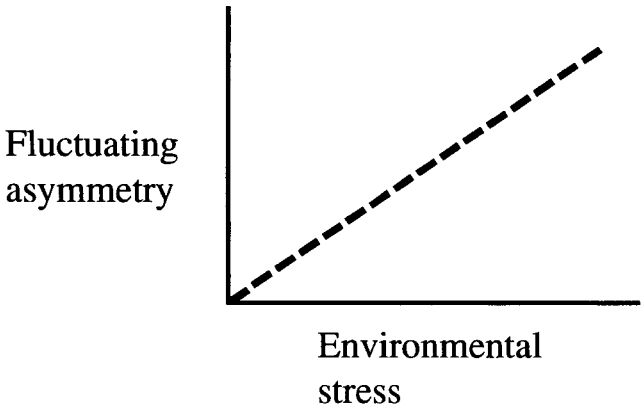

Fig. 1. Fluctuating asymmetry in a given individual may be increased by higher levels of environmental stress during development.

mental stability or the so-called out-breeding depression seen in some hybrids [reviewed by Graham, 1992; Clarke, 1993]. This mechanism may also explain the decreased symmetry seen in disorders like Down syndrome [Barden, 1980a; Shapiro, 1983] and fragile X syndrome [Peretz et al., 1988]. Indeed, decreased developmental stability may be a common characteristic of aneuploidy [Shapiro, 1975, 1992; Colacino and Petterson, 1978; Bersu, 1980]. The observation that "traits less buffered than others in the general population are the ones most disturbed" in Down syndrome [Shapiro, 1983] suggests that anauploidy may result in an overall decrease in developmental homeostasis, rather than a limited disruption of specific pathways. The critical point with all of these mechanisms is that there is no genetic program directing one side of the body to become larger than the other (see Palmer and Strobeck [1986, 1992] for further discussion); in the absence of any environmental stress all individuals should develop perfect bilateral symmetry. This relationship is illustrated in Figure 3.

In contrast, when the literature downplays the importance of a genetic component of fluctuating asymmetry [Livshits and Smouse, 1993b; Arrieta et al., 1993; Burke and Healy, 1993; Livshits et al., 1988a,b; Bailit et al., 1970; Holt, 1954; Singh, 1970], reference is more correctly being made to a genetically programmed

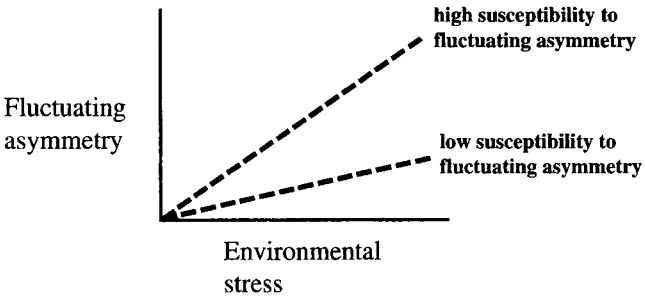

Fig. 2. The same relationship as illustrated in Figure 1, but here with two different genotypes: one with a high susceptibility to fluctuating asymmetry and another with a low susceptibility to fluctuating asymmetry. At a given level of environmental stress, the genotype possessing greater susceptibility will show a greater asymmetry.

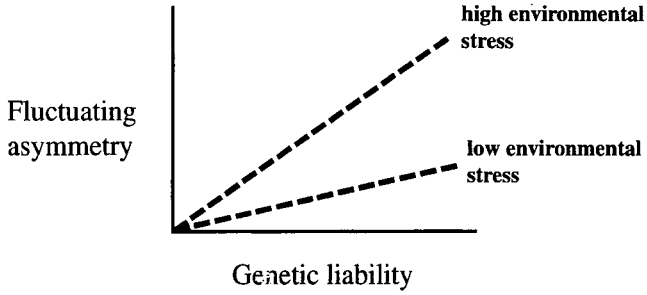

Fig. 3. Fluctuating asymmetry may be increased in individuals with a high genetic liability (high homozygosity or high number of disease specific alleles). However, for a given genetic liability, the resulting asymmetry also depends on the level of environmental stress the individual experienced during development.

asymmetry which would be present even in the absence of any environmental stress. By definition, only environmentally induced asymmetry can be considered true fluctuating asymmetry [Palmer and Strobeck, 1986]. It should also be noted that the definition of fluctuating asymmetry does not include the often striking asymmetries due to uterine factors such as trauma, tumors, or amniotic band disruptions; for a discussion of this topic refer to reviews by Cohen [1995a,b].

POTENTIAL OF FLUCTUATING ASYMMETRY AS A RISK MARKER

In order for fluctuating asymmetry to predict the appearance of developmental disorders, one or both of the following conditions must be met:

1. The environmental stress that caused a breakdown in developmental stability also contributed to the appearance of the disorder.
2. The genetic predisposition (liability) to the disorder and increased susceptibility to fluctuating asymmetry have a common cause.

These relationships are illustrated in Figure 4. Because this model predicts that the level of fluctuating asymmetry may vary among affected individuals, fluctuating asymmetry may have a poor sensitivity as screening tool and would be a useful diagnostic predictor of disease only in those individuals who are the most asymmetric.

A further observation with potential implications of clinical significance is that increased fluctuating asymmetry has been noted not only in some affected individuals, but also in family members of affected individuals [Woolf and Gianas, 1976, 1977; Livshits et al., 1988a,b]. This raises the possibility that fluctuating asymmetry may have implications in genetic counselling. At first glance, this may appear paradoxical because it requires that fluctuating asymmetry be heritable (but recall that fluctuating asymmetry is the result of environmental insults and does not have a genetic component). The answer, again, is that it is not fluctuating asymmetry itself, but rather susceptibility to fluctuating asymmetry that is being inherited (refer to Fig. 1). Although this point was raised by Sofaer [1979], it has not been adequately addressed in subsequent papers dis-

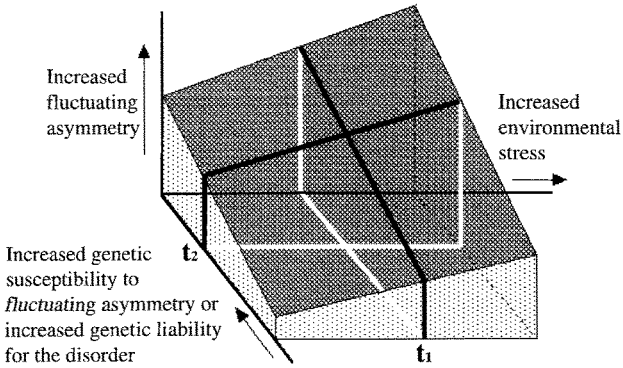

Fig. 4. Possible relationships between environmental stress, genetic liability and fluctuating asymmetry. Two scenarios are shown. In the first, t_1 represents a threshold of environmental stress above which a given disorder occurs. Here environmental stress contributes both to the appearance of disease and to the breakdown of developmental stability (appearance of increased fluctuating asymmetry). The actual observed level of fluctuating asymmetry, however, also depends on the genetic susceptibility to fluctuating asymmetry. Therefore, a range of asymmetries in affected individuals are possible. In the second scenario, the Z-axis represents the genetic liability for disease. Here the genetic liability and susceptibility to fluctuating asymmetry have a common basis. The threshold t_2 represents the level of genetic liability above which a given disorder occurs. Again, affected individuals exhibit a range of fluctuating asymmetries, this time depending on the level of environmental stress to which they were exposed.

cussing the heritability of fluctuating asymmetry in humans.

If susceptibility to fluctuating asymmetry does have a heritable component, what is the mode of inheritance? It is easy to imagine how trait-specific alleles could be inherited. Individuals that received a large number of deleterious recessive alleles (a high liability) would as a consequence be less symmetrical, thus producing a measurable heritability in fluctuating asymmetry. The other putative cause, heterozygosity, would traditionally not be considered heritable. Despite this perception, several authors have recently suggested that heterozygosity can be heritable under certain conditions (see Watson and Thornhill [1994] for discussion).

With the exception of Hagen [1973], the observed heritabilities of fluctuating asymmetry in animal models are often vanishingly small [Reeve, 1960; Mason et al., 1976; Ehrman et al., 1978; Leary et al., 1985]. In humans, few examples are available but values of 5–40% for dermatoglyphic characters have been reported [Singh, 1970; Arrieta et al., 1993]. Bailit et al. [1970] reported heritability for fluctuating asymmetry of dental characters of 2–5%. Likewise, Livshits and Kobyliansky [1989] reported that heritability for fluctuating asymmetry in eight morphometric traits was generally in the range of 0–28%. Interestingly, when all eight traits were considered together, heritabilities were considerably higher, ranging from 22.4–33.4%. Thus, potentially low heritabilities introduces another source of variation in addition to those already discussed. But because high liabilities for disease and high susceptibility to fluctuating asymmetry may go together, we might expect to see a higher heritability of fluctuating asymmetry in families with a history of genetic or developmental diseases. This has yet to be directly tested, but it could explain why a significant heritability has been found in work on affected individuals [Arrieta et al., 1993], while studies of presumably healthy individuals have calculated heritabilities that are lower [Singh, 1970] or lacking [Holt, 1954]. Unfortunately, there are no studies on multivariate fluctuating asymmetry in individuals with genetic disorders with which to compare the work of Livshits and Kobyliansky [1989].

A further point regarding the connection between fluctuating asymmetry and liability concerns the topic of liability itself. We have, so far, been treating liability as a single etiological agent producing a single clinical outcome. In reality, humans probably possess varying sub-threshold liabilities for numerous multifactorial diseases. Whether these act independently to disrupt developmental homeostasis or in additive fashion awaits investigation. Indeed, the presence of various sub-threshold liabilities may be a significant additional source of variation in studies of fluctuating asymmetry and genetic liability.

Lastly, researchers and clinicians wishing to explore the diagnostic potential of fluctuating asymmetry must decide which traits will be measured. It has already been mentioned that characters which are found to possess significant degrees of directional or antisymmetry should not be used. The practice of 'correcting for' directional asymmetry or antisymmetry by arithmetically adjusting means to zero (e.g., Livshits et al. [1988a]) has been criticized as not addressing the underlying genetic component of directional asymmetry [Palmer and Strobeck, 1992]. Techniques for detecting other types of asymmetry in addition to fluctuating asymmetry are given in Palmer and Strobeck [1992]. Traditionally dermatogyphics and odontometrics have been the characters most commonly used in studies on human populations. Each of these approaches have had proponents [e.g., Bailit et al., 1970; Kieser et al., 1986; Livshits and Kobyliansky, 1987]; however no character has proved ideal. Smith et al. [1982] suggested that many of the published population differences in dental asymmetry could be explained by sampling effects stemming from the small sample sizes used. Measurement error itself can also mimic fluctuating asymmetry [Watson and Thornhill, 1994], and along with sampling effects may "swamp" any true fluctuating asymmetry if average asymmetries are small [Smith et al., 1982]. Dental asymmetries suffer from the additional problem of a prolonged developmental time frame, thus decreasing the potential for linking increased fluctuating asymmetry to a discrete developmental event. Dermatoglyphics, in contrast, are determined at about 10 weeks of gestation [Penrose and Ohara, 1973] and therefore reflect only events occurring in early development. Other researchers have examined fluctuating asymmetry in anthropometric traits (e.g., ear length, foot breadth, palm breadth, and facial asymmetry) [Malina and Buschang, 1984; Livshits et al., 1988a; Livshits and Kobyliansky, 1989; Livshits and Smouse 1993a,b; Burke and Healy, 1993]. Again the problem

with interpreting fluctuating asymmetry in this context is the long developmental time of these traits. Furthermore, it is unclear if fluctuating asymmetry in specific anthropometric traits remains constant as the individual grows, although it may in other species [Chippindale and Palmer, 1993]. Skeletal traits have not been extensively explored, despite the publication of methodology for quantifying fluctuating asymmetry from hand radiographs [McLeod and Coupland, 1992]. However, it would seem as if skeletal characteristics would suffer from many of the same problems as other anthropometric landmarks already commonly used.

Where possible, assessment of fluctuating asymmetry in multiple traits [Livshits et al., 1988a; Livshits and Kobyliansky, 1989; Zhirotovsky, 1992] probably provides a better estimate of developmental homeostasis that single variable estimates, due to variation in the extent that different traits express fluctuating asymmetry [Polak, 1993; Livshits and Smouse, 1993b; Livshits et al., 1988a,b]. Clarke [1993] proposed that this variation could be mediated by measuring traits which have a functional basis for symmetry, and in which minor asymmetries do not have large effects on individual fitness. It is clear that none of the commonly used characters in humans meets all of the criteria suggested in the above discussion.

In conclusion, although increased fluctuating asymmetry has been shown in a number of disorders, the full potential of fluctuating asymmetry as a risk marker for disorders of developmental origin has yet to be determined. In this paper, we provided a review of previous studies and suggested a theoretical framework in which to view the relationships between fluctuating asymmetry and developmental disorders. To facilitate the future assessment of fluctuating asymmetry as a risk marker, future studies should present odds ratios in addition to the traditional group comparisons. This final point will be further explored by the authors in a future paper.

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